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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/746,635	11/13/96	MURTHY V	96700/341

HM12/0330

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EXAMINER	
GABEL, G	
ART UNIT	**PAPER NUMBER**
1641	20

DATE MAILED: 03/30/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/746,635	Applicant(s) Murthy et al.
	Examiner Gailene R. Gabel	Group Art Unit 1641

☒ Responsive to communication(s) filed on *Dec 21, 1998* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *20-23* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *20-23* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☒ The proposed drawing correction, filed on *Jul 16, 1997* is ☒approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Informalities

1. Applicants' request to cancel claims 1-4, 8-10, and 19 and to add claims 20-23 on Paper No. 13 on 12/28/98 is acknowledged. Accordingly, claims 1-4, 8-10, and 19 have been canceled. Claims 20-23 have been entered.

Claim Rejections - 35 USC § 112

2. Applicants have modified claims 1-3 and 19 to reflect claims 20-23 respectively, in order to correct a previous 35 USC 112, second paragraph rejection. Accordingly, the rejection has been overcome.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claim 20 (corresponding to canceled claim 1) is rejected under 35 U.S.C. 103(a) as being unpatentable over Olsson et al. (Journal of Applied Biochemistry, 5:437-445 (1983)) for reasons of record.

5. Claims 21-23 (corresponding to canceled claims 2-3 and 19) are rejected under 35 U.S.C. 103(a) as being unpatentable over Olsson et al. (Journal of Applied Biochemistry. 5:437-

445(1983)) as applied to claim 20 above, and further in view of Tsuji et al. (Chemical Abstract 86:39099) or Friedrich et al (Biochemical Genetics, 22 (5/6): 389-394(1984)) and if necessary, further in view of Buth et al. (Biological Abstract 71059076 (1981)) for reasons of record.

Response to Arguments

6. Applicants argue that (1) Olsson et al. describe an assay for determining the aging of blood for transfusion purposes which is from a "closed or controlled environment", thereby limiting the measure of the release of adenylate kinase only to aging erythrocytes and therefore lacking the teaching of other origins of adenylate kinase. Applicants refer to serum as sample taken from the human body and differs from Olsson's plasma which is blood stored for transfusion purposes. (2) Tsuji et al., Friedrich et al., Buth et al., and Matsuura et al., do not distinguish erythrocyte adenylate kinase from other origins in a serum sample. (3) Combining all aforementioned references does not render obvious a method for diagnosing erythrocyte hemolysis in a serum sample.

In response to argument (1), it is respectfully submitted that Olsson et al. does distinguish that portion of total adenylate kinase which is due to erythrocyte adenylate kinase from adenylate kinase of other origins via addition of DAPP, which is specific inhibitor of erythrocyte adenylate kinase (see page 442, paragraph 3). Olsson explicitly states that DAPP is a **specific inhibitor of erythrocyte adenylate kinase**, not platelet adenylate kinase. Olsson clearly suggests the critical correlation of hemolysis and erythrocyte adenylate kinase. Contrary

to applicants' argument, blood for transfusion from which plasma is derived, is drawn from a human being and is stored in a sterile blood container for future use. Save from the addition of anticoagulants in blood for transfusion, plasma and serum from the same human being would otherwise have the same constituents, i.e. adenylate kinase from erythrocytic origin, and muscular and hepatic origin, if present. However, Olsson's study was drawn to measuring hemolysis from blood bag samples so that the use of DAPP in Olsson's assay to distinguish the origin of adenylate kinase as erythrocytic, as opposed to other origins, such as platelets, is therefore, relevant. Furthermore, while the present invention is drawn to measuring level of in vivo hemolysis from physiologic or pathologic causes in patients, Olsson was studying in vitro hemolysis of aging erythrocytes from leakage of adenylate kinase from stored blood cells. Both inventions are drawn to measuring erythrocytic adenylate kinase which is a measure of enzymatic activity and both correlate directly to hemolysis, regardless of whether the phenomenon of hemolysis occurred in vivo or in vitro. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Olsson et al. by determining erythrocyte adenylate kinase activity in serum rather than plasma because serum and plasma are conventional alternative sample types used in clinical analysis, differing only in the presence or absence of anticoagulation.

(2) Insofar as Tsuji et al. teaches electrophoretic separation and visual definition/ detection of the adenylate kinase isoenzymes, i.e. adenylate kinase from different cellular sources such as muscle and liver, it is respectfully submitted that Tsuji suggests determination of

erythrocyte adenylate kinase levels by agarose thin-layer gel electrophoresis. Friedrich et al. describe electrophoretic separation and visualization of **human erythrocyte adenylate kinase** and further shows "Histochemical staining of human erythrocyte adenylate kinase" in Figure 2. Buth et al. does not specifically address adenylate kinase isoenzymes; however, one of ordinary skill in the art at the time of the invention would have found that suggestion implicit in Buth et al. by virtue of (1) the reference to "electrophoretic" staining procedures, and (2) the references to enzymes commonly resolved by electrophoresis into their isoenzymes, e.g. creatine kinase. Finally, Matsuura et al. teach separation of adenylate kinase isoenzymes, e.g. AKI (erythrocyte adenylate kinase), by column chromatography prior to determination of the enzymatic activity of each fraction eluted from the column. Therefore, it would have been obvious and well within ordinary skill in the art to measure erythrocyte adenylate kinase by known and conventional assays for differentially measuring isoenzymes, including electrophoretic separation and staining, such as with NAD-dependent glucose-6-phosphate dehydrogenase (G6PD) visualization technique, immunoassays, etc. as suggested by Tsuji et al., Friedrich et al., Buth et al. and/or Matsuura et al.

(3) The Court of Appeals for the Federal Circuit Court in Interconnect Planning Corp., 227 USPQ 543 (Fed. Cir. 1985), stated that "not only must the claimed invention as a whole be evaluated, but also must the references as a whole, so that their teachings are applied in the context of their significance to a technician at the time." Id. At 551. A person with ordinary skill in the art at the time would have appreciated the correlation between hemolysis and erythrocyte

adenylate kinase suggested by Olsson et al. and emphasized by the parallel between hemoglobin (a known indicator of hemolysis) and erythrocyte adenylate kinase taught by Olsson et al.; as well as the ability to measure the erythrocytic isoenzyme of adenylate kinase, e.g. using ordinary and conventional means for differentially measuring isoenzymes, such as immunoassays and electrophoretic separation, commonly used to differentially measure over isoenzymes, including creatine kinase and lactate dehydrogenase isoenzymes which are basic techniques known by those well within ordinary skill in the art at the time of the invention.

The arguments are not persuasive for the above reasons and reasons of record. Therefore, no claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R, Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday from 7:00 AM to 4:30 PM. The examiner can also be reached on alternate Fridays at 7:00 to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gailene R. Gabel
Patent Examiner
Art Unit 1641
March 18, 1999

James C. Housel
JAMES C. HOUSEL 3/27/99
SUPERVISORY PATENT EXAMINER